

## Synthesis of Aryl 2-Benzofuranyl and Aryl 2-Indolyl Carbinols of High Enantiomeric Purity *via* Palladium-Catalyzed Heteroannulation of Chiral Arylpropargylic Alcohols

Maurizio Botta\*, Vincenzo Summa, Federico Corelli\*, Giovanna Di Pietro§ and Paolo Lombardi§

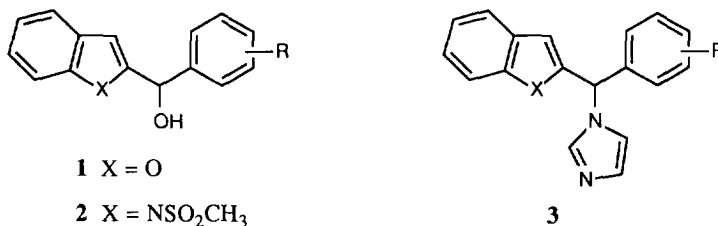
Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, I-53100 Siena-Italy.

§Menarini Ricerche Sud SpA, Via Tito Speri 10, I-00040 Pomezia (Roma)-Italy.

**Abstract** : 2-Iodophenol and 2-iodo-*N*-mesylaniline have been reacted with  $\alpha$ -arylpropargylic alcohols of high enantiomeric purity under transition-metal catalysis leading to aryl 2-benzofuranyl and aryl 2-indolyl carbinols in good yield and high enantiomeric excess, thus constituting the first enantiospecific synthesis of these important classes of compounds.

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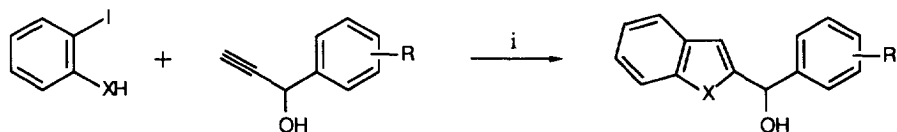
Molecules with benzo[b]furan (1-benzofuran) and indole substructures are occurring widely both in natural products and in biologically active synthetic compounds.<sup>1,2</sup> Numerous synthetic approaches to these compounds have been developed,<sup>3</sup> among which the transition-metal (particularly palladium) mediated cycloaddition reactions of alkynes are currently investigated by several groups.<sup>4</sup>



In connection with previous studies,<sup>5</sup> we turned our attention to the synthesis of enantiomerically pure aryl 2-benzofuranyl carbinols **1** and aryl 2-indolyl carbinols **2** as precursors of azole compounds **3**, whose racemates have been shown to display antifungal<sup>6</sup> and aromatase inhibiting<sup>7</sup> activities. In 1992 Kundu *et al.* reported<sup>8</sup> the preparation of some racemic **1** in good yield by reacting the appropriate propargylic alcohols (100% excess) with 2-iodophenol in the presence of (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>, CuI and triethylamine in DMF. It remained unclear, however, whether this method could also be adapted to the preparation of enantiomerically pure derivatives **1**. Experiments of this nature are described below (Scheme, Table).

In typical experiments 2-iodophenol (1 mmol) was stirred with 1-phenyl-2-propyn-1-ol (1 mmol) in the presence of bis-triphenylphosphine palladium(II) chloride (0.025 mmol), CuI (0.025 mmol), and tetramethylguanidine (TMG, 3 mmol) in DMF at 40 °C for 4 h while passing argon through the solution. After dilution with water the mixture was extracted with ethyl acetate and the crude product was purified by column chromatography (silica gel/dichloromethane) to give compound **1a** in 91% yield.<sup>9</sup>

## Scheme



For R and stereochemistry see Table.

i. Reaction conditions:  $(\text{PPh}_3)_2\text{PdCl}_2$ , CuI, TMG, DMF, 40 °C, argon.

1 X = O

2 X = NSO<sub>2</sub>CH<sub>3</sub>

**Table. Palladium-mediated Cyclization of Propargylic Alcohols to Heterocyclic Derivatives 1 and 2**

Entry	Product	R	Reaction time (h)	Yield (%) <sup>a</sup>	Configuration	$[\alpha]_{\text{D}}^{20\text{b}}$	ee (%) <sup>c</sup>
1	<b>1a</b>	H	4	91	<i>R,S</i>		
2	<b>1b</b>	H	4	90	<i>S</i>	+16.9 (c 1.18)	97.5
3	<b>1c</b>	<i>m</i> -Me	3	92	<i>R,S</i>		
4	<b>1d</b>	<i>m</i> -Me	3	93	<i>R</i>	-3.6 (c 2.81)	98.1
5	<b>1e</b>	<i>p</i> -F	2.5	78	<i>R,S</i>		
6	<b>1f</b>	<i>p</i> -F	2.5	79	<i>R</i>	-5.7 (c 1.75)	97.7
7	<b>2a</b>	H	1	87	<i>R,S</i>		
8	<b>2b</b>	H	1	87	<i>S</i>	+22.3 (c 2.02)	96.7
9	<b>2c</b>	<i>m</i> -Me	3.5	93	<i>R,S</i>		
	<b>2d</b>	<i>m</i> -Me	3.5	93	<i>R</i>	-16.7 (c 1.50)	99.1
11	<b>2e</b>	<i>p</i> -F	1.5	79	<i>R,S</i>		
12	<b>2f</b>	<i>p</i> -F	1.5	78	<i>R</i>	-24.5 (c 2.45)	98.0

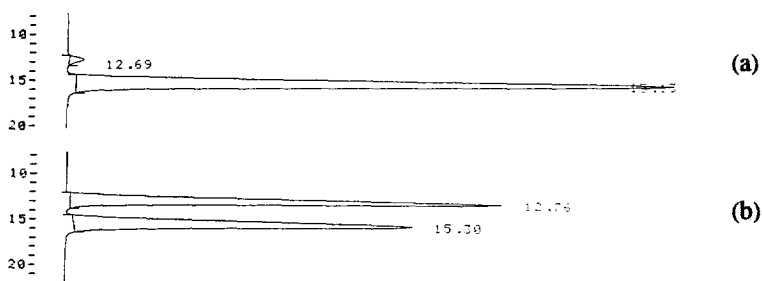
<sup>a</sup>Not optimized yields referring to isolated and purified materials. <sup>b</sup>Measured in chloroform solution.

<sup>c</sup>The enantiomeric excess (ee) was determined by HPLC on a DAICEL CHIRALCEL OD column.

Subsequent application of this procedure to (*R*)-(-)-1-phenyl-2-propyn-1-ol (entry 2) led to the corresponding benzofuran derivative **1b** in 90% yield. HPLC analysis on a DAICEL CHIRALCEL OD column (250x4.6 mm) eluting with *n*-hexane/isopropanol 80/20 (flow rate 0.8 ml/min) in comparison with the chromatogram of racemic **1a** gave an enantiomeric excess (ee) of 97.5%. Based on the assumption that the stereogenic centre in the starting alcohol is not affected during this transformation, the absolute stereochemistry of (*S*)-**1b** can be assigned.

Other racemic and enantiopure<sup>10</sup> propargylic alcohols have been subjected to the same heteroannulation reaction with 2-iodophenol (entries 3-6) to give the corresponding benzofuran derivatives **1c-f** in good yield and

with high enantiomeric excess. This procedure also works very well when applied to 2-iodo-*N*-mesylaniline (entries 7-12), leading to racemic and enantiomerically pure aryl 2-indolyl carbinols **2a-f**. The enantiomeric excess of compounds **1d,f** and **2b,d,f** was again determined by chiral HPLC using the same conditions as reported for **1b** (compare Figure), while the absolute configurations were assigned based on those of the corresponding propargylic alcohol.<sup>10</sup> It should be pointed out that the enantiomeric excess of the resulting product was always identical with that of the corresponding starting material, thus demonstrating the complete stereospecificity of the reaction.



**Figure.** Chromatogram of (*S*)-**2b** (a) in comparison with (*RS*)-**2a** (b) (DAICEL CHIRALCEL OD column 250x4.6 mm, eluant: *n*-hexane/isopropanol 85/15, flow rate: 1 ml/min).

In conclusion, we have developed the first enantiospecific synthesis<sup>11</sup> of chiral aryl heteroaryl carbinols in very high chemical yield and enantiomeric excess. It is also worth noting that, in contrast to Kundu's procedure, our methodology uses only stoichiometric amounts of the valuable enantiopure alcohols.

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  - 9) Not optimized yields refer to isolated and purified materials. All the new compounds gave satisfactory microanalyses and showed spectroscopic data in accordance with the assigned structures.
  - 10) For the preparation of these enantiomerically pure propargylic alcohols, see the preceding paper in this issue.
  - 11) Attempts to prepare compounds **1** by enantiospecific reduction of the corresponding ketones were unsuccessful.

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